

REMARKS

Claims 2, 3, 12, 13, and 18-41 have been canceled. Claims 1, 4, 5-11, 14-17, and 42 have been amended. Claims 43-48 are new. The amended and new claims are supported throughout the application as filed, e.g., at page 5, line 28 through page 6, line 15; at page 15, lines 9-11, and by the original claims. Upon entry of this amendment, claims 1, 4-11, 14-17, and 42-48 will be pending and under examination.

Information Disclosure Statement

In accordance with the Examiner's request (see the Office action at page 2), copies of the majority of the references submitted by Applicants on April 11, 2002, are provided herewith. A copy of reference AXX (Kim, et al. *Targeting the IL-15 Receptor with an Antagonist IL-15/Fc γ 2a Protein Blocks DTH and Enhances the Acceptance of Islet Allografts*. 17th ASTP (Physicist) Annual Meeting, Chicago, IL May 9-13, 1998 (p. 713)) will be submitted shortly under separate cover. Copies of the Information Disclosure Statement and Form PTO-1449 submitted on April 11, 2002 are also enclosed.

35 U.S.C. § 112, first paragraph

Enablement

Claims 1-11, 13-17, and 42 were rejected on the ground that they are non-enabled. The Examiner stated (Office action at page 3) that the specification:

does not reasonably provide enablement for 'all' possible compositions comprising a first agent that targets an IL-15 receptor and a second agent that inhibits 'all' possible costimulatory signals transmitted between a T cell and an antigen-presenting cell (APC)

In view of the present amendment, and the remarks that follow, this ground for rejection should now be withdrawn. Claim 1, as amended, no longer covers all of the possible compositions the Examiner describes above. To the contrary, claim 1 now covers only a therapeutic composition that includes a specific IL-15 mutant polypeptide (one comprising SEQ ID NO:4 with a mutation at position 149 and/or position 156). The composition must also include a polypeptide that binds a B7 molecule. One of ordinary skill in the art could certainly make such polypeptides without resort to undue experimentation. Applicants teach how to construct IL-15 mutant

polypeptides in detail (*see, e.g.*, page 24, line 25 to page 25, line 16; *see also* page 18, lines 24-32). Moreover, polypeptides, including those required by the present claims, can be generated using conventional molecular biology techniques (including PCR-assisted mutagenesis). Applicants recognized that polypeptides other than those exemplified could be made and used; Applicants stated, for example, that their techniques could "be used to incorporate any other amino acid in place of the glutamine residues at positions 149 or 156 or to introduce amino acid substitutions at positions other than 149 and/or 156" (page 25, lines 14-16). With respect to polypeptides that bind B7, Applicants described the CTLA4/Ig polypeptide (which the Examiner found enabled) and anti-B7 antibodies (*see, e.g.*, page 8, lines 8-12). One of ordinary skill in the art would not have to resort to undue experimentation to make either a mutant IL-15 polypeptide (as claim 1 now requires) or a polypeptide that binds B7 (which is similarly required).

Moreover, the specification describes some of the assays available for evaluating any of the mutant IL-15 and B7-binding polypeptides one can readily make. Applicants teach, for example, that mutant IL-15 polypeptides include those that "compete effectively with wild-type IL-15 polypeptides and can inhibit one or more of the events that normally occur in response to IL-15 signaling, such as cellular proliferation" (page 4, lines 25-27; *see also* the following text to page 6, line 21, and page 24, lines 19-22). Assays that can be used to determine whether a given composition includes effective polypeptides are known in the art and clearly described in the specification. For example, Applicants describe methods to assay cellular proliferation (*see, e.g.*, page 25, lines 18-27, where assays to examine proliferation of BAF-BO3 cells and human peripheral blood mononuclear cells (PBMCs) are described; *see also, e.g.*, page 25, line 29, through page 26, line 4, where an assay to detect binding of derivative IL-15 polypeptides to various cell lines is described). Thus, one of ordinary skill in the art would have no need to resort to undue experimentation to assess the functional properties of compositions that include the claimed mutant IL-15 polypeptides.

With respect to claim 10, Applicants ask the Examiner to note that, as this claim now depends from claim 1, it is limited to a composition that includes the mutant IL-15 polypeptide described in claim 1 having (as further required by claim 10) "a moiety that leads to the elimination of IL-15R-bearing cells." The Examiner recognizes that the "instant specification discloses an IL-15 mutant with an Fc region that might have a cytotoxic activity." Indeed,

Applicants described Fc regions that can deplete cells in the specification (*see, e.g.*, page 7, lines 7-23); Fc regions are known in the art, as are other moieties that eliminate targeted cells (in the present invention, the moiety of claim 10 is targeted to an IL-15R-bearing cell by virtue of its association with the mutant IL-15 polypeptide). Given Applicants' teaching, their examples, the new breadth of the claim, and the level of skill in the art, one would not be forced to rely on undue experimentation to practice the invention covered by Applicants' claim 10.

Claim 42, which covers a method of making the therapeutic composition of claim 1, is also enabled. For the reasons stated above in the discussion of claim 1, one of ordinary skill in the art can readily make the limited polypeptides now required; methods of expressing and purifying polypeptides are well known in the art.

Written Description

Claims 1-11 and 13-17 were rejected as lacking an adequate written description (Office action at pages 5-7).

Claim 1 (from which the remaining pending and rejected claims depend) has been amended as described above. The scope of the claim has been narrowed considerably to cover compositions that include a mutant IL-15 polypeptide that has a mutation at one or both of positions 149 and 156 of SEQ ID NO:4 and a polypeptide that binds B7. Given the teachings of the specification, Applicants have conveyed "with reasonable clarity" that they were in possession of the invention now claimed (and, in accordance with the law reviewed by the Examiner, meet the standard for an adequate written description; see the standard set out in *Vas-Cath Inc. v. Mahurkar*). More specifically, Applicants wish to respond to the Examiner's allegation that the specification discloses a single mutant having glutamine to aspartate mutations at positions 149 and 156 of SEQ ID NO:2. This is not true. *See*, for example, page 5, line 32, where Applicants teach that "the mutant IL-15 polypeptide can differ from wild type IL-15 by the addition, deletion, or substitution of a single amino acid residue, for example, an addition, deletion, or substitution of the residue at position 156." As the claims require that the mutant IL-15 polypeptide "target an IL-15 receptor", and the claims also require mutations in specific residues of the polypeptide, it is clear that Applicants examples and description in the specification adequately describes the claimed genus.

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35 U.S.C. § 112, second paragraph

The Examiner rejected claim 2 as indefinite for reciting a "substantially pure [IL-15] mutant" (Office action bridging pages 7-8). Although claim 2 has been canceled, this term has been incorporated into claim 1. Applicants have provided guidance as to the meaning: Applicants state that a substantially pure polypeptide "is at least 60% by weight (dry weight) the polypeptide of interest" (page 18, lines 5-11). Applicants submit that this definition is clear; inclusion of the term "substantially pure mutant" does not prevent one of ordinary skill in the art from recognizing the metes and bounds of claim 1.

The Examiner rejected claim 42 as incomplete because the claim "does not recite what the expression systems comprise, and how to combine the two polypeptides" (Office action at page 8). More specifically, the Examiner asks, "[i]s simply mixing the two polypeptides sufficient to make the desired composition?" Claim 42, as amended, is directed to a method of making a composition using expression systems that comprise cells, where the cells include a nucleic acid encoding the agents of the composition. With respect to combining the two polypeptides, the two polypeptides may be simply mixed, as the Examiner suggested. Conditions that are not specified are in accordance with industry practice (otherwise, no therapeutically useful composition would result). Should the Examiner continue to believe the claim language is unclear, the favor of a telephone call to the undersigned (to discuss alternative terms) is requested.

Enclosed is a \$465.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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